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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: GENERAL APPROACH TO ESTABLISH AN ACUTE REFERENCE DOSE (ARfD)

Guidance for Industry

VICH GL54

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For Implementation at Step 7

STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: GENERAL APPROACH TO ESTABLISH AN ACUTE REFERENCE DOSE (ARFD)

Adopted at Step 7 of the VICH Process by the VICH Steering Committee in November 2016
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This Guidance has been developed by the appropriate VICH Expert Working Group and has been subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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GUIDANCE FOR INDUSTRY

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1. *Introduction*

1.1 Objective

The current guidance addresses the nature and types of data that can be useful in determining a toxicological acute reference dose (ARfD) for residues of veterinary drugs, the studies that may generate such data, and how the ARfD may be calculated based on these data.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

1.2 Background

The safety of residues of veterinary drugs in human food is most commonly addressed through the conduct of toxicology studies in test animal species that provide for the determination of a no-observed-adverse-effect level (NOAEL)[1] and an acceptable daily intake (ADI) by application of appropriate safety/uncertainty factors (UF(s)).[2] The ADI, generally expressed as microgram (µg) or milligram (mg)/kg body weight per day, is defined as the daily intake which, for up to an entire lifetime, appears to be without adverse effects or harm to the health of the consumer (see Glossary).

It has been recognized that there is the potential for some veterinary drug residues to cause adverse effects in the human consumer following a single meal. The ADI may not be the appropriate value in such cases for quantifying the level above which exposure after a single

[1] Both the terms NOEL (no-observed-effect level) and NOAEL (no-observed-adverse-effect level) have historically been used to establish an ADI. In practice, NOEL and NOAEL have had similar meanings when used for this purpose.

[2] While some regulatory authorities use the term "safety factor" and others use the term "uncertainty factor," there is a general agreement in the application of these terms to address variability between groups (e.g., from animal models to humans) and within groups (e.g., animal to animal or human to human variability). For the purpose of this document, UFs will be used to represent the use of either safety or uncertainty factors.

meal or over one day can produce acute adverse effects. Determining the ARfD is an appropriate approach to address this concern.

The ARfD approach has been developed to provide a human health guidance value for pesticides and other chemicals, including veterinary drugs, when their use can result in residues high enough to cause adverse effects following acute or short-term exposures in people consuming large portions of food containing the residue. This contrasts with the use of ADIs, which are established to address potential adverse effects following chronic or long-term exposures to residues in foods.

Various publications which describe the ARfD approach are available. In 2005, some members of the United Nations Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Meeting on Pesticide Residues (JMPR) published a paper describing the development of the ARfD for acute health risk assessment of agricultural pesticides (Solecki *et al.*, 2005). The Organization for Economic Co-Operation and Development (OECD) has finalized Guidance No. 124, "Guidance for the Derivation of an Acute Reference Dose," which is primarily intended for pesticides, biocides, and veterinary drugs (IOMC, 2010). The OECD Guidance No. 124 describes a tiered approach that is intended to maximize the use of available data and minimize the need for studies specifically designed to derive an ARfD. This approach is consistent with the 3-Rs (Replacement, Refinement and Reduction) minimizing the use of animals in the development of veterinary drugs. In addition, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has noted that "certain substances ….. *e.g.*, some metals, mycotoxins, or veterinary drug residues, could present an acute risk, *i.e.*, could raise concern regarding acute health effects in relation to short periods of intake at levels greater than the ADI or TDI[3]." JECFA agreed that, "building on the experience of and the guidance developed by JMPR ….. the need to establish an ARfD should be considered on a case-by-case basis, and only if the substance, on the basis of its toxicological profile and considering the pattern of its occurrence and intake, is likely to present an acute health risk resulting from exposure in a period of 24 h or less" (JECFA, 2005). JECFA and JMPR have contributed to the International Program on Chemical Safety (IPCS) Environmental Health Criteria (EHC) 240 describing the derivation of an ARfD in the application of a maximum residue limit (MRL), a tolerance, or other national or regional tools used to establish an acceptable concentration of residues of the veterinary drug in the edible tissues of treated animals (IPCS, 2009). In 2016, JECFA published a draft guidance for monographers on the use and interpretation of the ARfD. This document continues to be under development.

1.3 Scope of the current guidance

This guidance can be used to address the nature and types of data that should be useful in determining an ARfD, the studies that may generate such data, and how the ARfD can be calculated based on these data. The current guidance is limited to the application of toxicological and pharmacological endpoints and offers special consideration for residues of veterinary drugs in contrast to the available guidances and guidances that address the derivation and use of the ARfD for human exposure to pesticides, contaminants, and chemicals other than veterinary drugs. The guidance provides internationally harmonized technical recommendations

[3] TDI – tolerable daily intake.

for an ARfD used in support of veterinary product registration/approval. Detailed guidance on the derivation of an ARfD may be found in OECD Guidance 124 (IOMC, 2010).

This guidance does not, except in very broad terms, address

- When an ARfD would or would not be appropriate to address the concerns of a national or regional regulatory authority.
- Evaluation of specific pharmacological or toxicological adverse effects that may lead to the determination of an ARfD.
- Human dietary exposure data that may be appropriate for use with an ARfD in the derivation of an MRL, a tolerance or other national or regional tools used to refine an acceptable concentration of the veterinary drug residue in food.
- Refinement of the exposure calculation for the acute health risk assessment.
- Routes of human exposure to veterinary drugs other than the oral route.

Recognizing international efforts to address possible acute effects of residues of an antimicrobial veterinary drug on the human intestinal microbiota following acute human exposure, the current guidance only provides a harmonized approach to a toxicological ARfD at this time.

Finally, this guidance does not seek to limit the studies that can be performed to establish the safety of residues in human food with respect to acute toxicity. Neither does it preclude the possibility of alternative approaches that can offer an equivalent assurance of safety, including scientifically-based reasons as to why such data are not warranted.

2. *Guidance for an ARfD*

2.1 Stepwise procedure

Before examining the endpoints of acute pharmacological effects and toxicity, and before designing studies, careful consideration should be given to the 3-Rs principles. Therefore, the following stepwise approach is recommended before conducting an acute toxicity study:

- Step 1. Evaluate available pharmacological and toxicological data and information, including data from repeated-dose toxicity studies, in order to establish whether or not acute endpoints (attributable to the first 24 hours of dosing) have been adequately addressed.

- Step 2. If additional acute toxicity information is needed, consideration to the 3-Rs principle should be given, for example, by integrating observations/examinations related to acute endpoints in planned standard toxicity studies.

- Step 3. If the two options in Steps 1 and 2 are insufficient to provide adequate information on acute endpoints, then a new, specifically designed toxicity study(ies) can be considered.

- See also the decision tree in Annex 1.

2.2 Information and studies to support an ARfD

The first consideration should be to examine available data and information that describe the physical, chemical, pharmacological, and toxicological characteristics of the veterinary drug. This information can be available from data provided to support human food safety as per VICH GL33 or through published peer reviewed literature. In addition the studies provided under VICH GL33 to support safety may provide useful information for the evaluation of acute toxicity endpoints that support the assessment of an ARfD. It is recommended that all information on a specific veterinary drug be considered in the derivation of a chemical specific ARfD.

2.2.1 Use of traditional repeat-dose toxicology studies

The following are key points for consideration when evaluating information regarding the potential for acute toxicity:

- In the absence of data to the contrary, all relevant indications of acute adverse pharmacological and toxicological effects observed in repeated-dose studies can be considered as potentially relevant to setting an ARfD.
- Particular emphasis should be given to observations and investigations at the beginning of repeated dose studies.

Examples of potential endpoints of acute toxicity in standard toxicity studies include those described in OECD Guidance No. 124 (see paragraphs 36 through 59) and in EHC 240 (see section 5.2.9.5). Endpoints could include, but are not limited to, haematoxicity, immunotoxicity, neurotoxicity, hepatotoxicity, nephrotoxicity, developmental effects, reproductive effects, pharmacological effects, and direct effects on the gastrointestinal tract as well as clinical findings. In keeping with the goal of reducing the number of animals for testing, in some cases, it may be possible to modify the standard toxicology study protocols to provide more relevant information for the assessment of the ARfD without compromising the original objective of the study. For example, a veterinary drug might be anticipated to cause acute haematological changes; the protocol for a repeat-dose oral toxicity study in rats could be modified to include satellite groups where blood is sampled from control and treated animals beginning on the first day through the first two weeks of dosing to evaluate whether this endpoint occurs after one or just a few doses. If no effects are observed in the high dose group then no further evaluation of the collected samples would be warranted. Further, in this example a lower bound for potential acute toxicity may be established based on the high dose group in the study. In addition to the endpoints mentioned in EHC 240, adverse effects observed at the beginning of the study should be taken into consideration.

Prior to modification of an existing protocol, consideration should be given to available data and information that describe the physical, chemical, pharmacological, and toxicological characteristics of the veterinary drug, including its possible mode of action (MOA). While the relevant dosing for assessment of an ARfD is anticipated to be an acute dose (a single dose or up to a single day's dosing), the timing for measurement of effects should be based on an understanding of available pharmacokinetics and pharmacodynamics of the veterinary drug. Particular emphasis should be given to observations and investigations at the beginning of the

repeat-dose study in the determination of potential acute toxicity. The inclusion of selected endpoints for the evaluation of acute toxicity beyond those described in the guidance documents should be considered on a case-by-case basis.

Consideration should be given to dose selection, numbers of animals, and the use of satellite groups. A high dose group within the repeat-dose toxicity study protocol that is relevant to concerns related to acute exposure to the human consumer could inform an ARfD evaluation. Elements of study design described in OECD Guidance No. 124, Annex 2, can be incorporated into modifications of an existing repeat-dose toxicity study. Dose selection is also critical when developing a point of departure (POD) for the derivation of the ARfD. The POD from the most sensitive endpoint relevant to human food safety in the most appropriate species should be used.

2.2.2 Acute studies

In some cases, an appropriate POD to determine an ARfD is not available from existing information. Studies intended to address chronic toxicity may not provide sufficient information to allow a robust estimate of the ARfD. In such cases, a single exposure study specifically designed to support an ARfD for a given veterinary drug may be warranted. In all cases, it is recommended that the design of an acute effect study specifically to derive an ARfD include consideration of all available relevant physical, chemical, pharmacological, and toxicological information, and also consider the MOA (particularly of the pharmacologically active substance) where relevant.

Specific guidance on the conduct of a single exposure toxicity study can be found in Annex 2 of OECD Guidance No. 124.

2.3 How to derive an ARfD

The basic approach for the derivation of an ARfD is based on the identification of an appropriate POD, or threshold, for the pharmacological or toxicological endpoint of concern. This is typically identified as a NOAEL dose or benchmark dose lower confidence limit (BMDL). The ARfD is determined by dividing this POD by an appropriate UF(s). The ARfD can be reported as an amount of the substance expressed on a per person or body weight basis (e.g., mg/person or mg/kg body weight)

$$ARfD = \frac{\text{POD}}{\text{UF}}$$

Where:

POD is the point of departure or threshold for pharmacological or toxicological effects of concern (see Glossary).

UF is an uncertainty or safety factor, or series of factors that typically account for considerations such as animal to animal variability, interspecies extrapolation, quality of data, severity of response, etc. (see Glossary). Additional recommendations on the selection of an appropriate

uncertainty factor (described as a chemical specific assessment factor) are provided in Step One of the Tiered-Approach for the Derivation of an appropriate ARfD in OECD Guidance No 124 (IOMC, 2010).

Consideration should be given to the discussion of uncertainty factors in OECD Guidance No. 124 (see page 21) and EHC 240 (see section 5.2.3). The selection of appropriate UFs for inter-species and human inter-individual variabilities should be considered based on available data. To provide for the quantitative incorporation of differences in the toxicokinetic/toxicodynamics for a chemical, the default 10-fold factor for inter-species variability and the default 10-fold factor for human inter-individual variability can be used. When available, chemical-specific UFs on one or more specific sources of variability could replace the default values to adjust sub-factors for inter-species and human inter-individual variabilities. If chemical specific toxicokinetic and toxicodynamic data are inadequate to justify data based UFs, consider any information (*e.g.*, quantitative structure-activity relationship (QSAR) or MOA, of closely related compounds) that would indicate reduced or increased uncertainty.

When an ARfD could be determined based on toxicological and/or pharmacological endpoints, the ARfD should be based on the endpoint that is most relevant for protecting public health.

3. *Glossary*

The following definitions apply for purposes of this guidance:

3-Rs Replacement, Refinement, Reduction. VICH is committed to approaches that reduce, refine or replace the use of laboratory animals (the 3Rs) while maintaining appropriate scientific standards. The 3Rs principles were first introduced in Russell and Burch's 1959 book, 'The principles of humane experimental technique'.

ADI Acceptable Daily Intake is the daily intake which, during up to an entire life of a human, appears to be without adverse effects or harm to the health of the consumer. The ADI most often will be set on the basis of the drug's toxicological, microbiological, or pharmacological properties. It is usually expressed in micrograms or milligrams of the chemical per kilogram of body weight per day.

ARfD Acute Reference Dose. An estimate of the amount of residues expressed on a body weight basis that can be ingested in a period of 24 h or less without adverse effects or harm to the health of the human consumer.

BMD Benchmark Dose. A dose of a substance associated with a specified low incidence of response, generally in the range of 1 to 10%, of a health effect, or a dose associated with a specified measure or change of a biological effect. See Benchmark Dose Software (BMDS) (US Environmental Protection Agency, 2015), and PROAST (National Institute for Public Health and the Environment (RIVM), 2014).

BMDL Benchmark Dose Lower Confidence Limit. A dose producing an appropriate, low, and measurable response at a defined lower bound response level based on the lower one-

sided confidence limit of a 95% confidence interval extrapolated from a line fitted to available data for an appropriate endpoint.

EHC Environmental Health Criteria. International Program on Chemical Safety (IPCS) documents that provide international critical reviews on the effects on human health and the environment of chemicals or combinations of chemicals, including veterinary drugs, as well as physical and biological agents.

IPCS International Program on Chemical Safety. A joint program of the World Health Organization, International Labor Organization and the United Nations Environment Programme.

MOA Mode of Action. A biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data. A mode of action describes key cytological and biochemical events, that is, those that are both measurable and necessary to the observed effect in a logical framework.

NOEL No Observed Effect Level. The highest administered dose that was observed not to cause an effect in a particular study.

NOAEL No Observed Adverse Effect Level. The highest administered dose that was observed not to cause an adverse effect in a particular study.

OECD Organization for Economic Co-operation and Development brings together the governments of various countries to support sustainable economic growth, boost employment, raise living standards, maintain financial stability, assist other countries' economic development and contribute to world trade.

POD Point of Departure. A reference point for hazard characterization; typically a point on a dose-response curve at which the response first becomes apparent, and represents toxicological or pharmacological effects of concern; often classified as a NOEL, NOAEL, or BMDL.

QSAR Quantitative Structure Activity Relationship. A quantitative relationship between a biological activity (e.g., toxicity) and one or more molecular descriptions that are used to predict activity.

Satellite Groups Additional groups of animals typically treated following all or some of the study treatment protocol and then examined for endpoints that differ from the main study group or are in other ways treated differently. For example, a satellite group of rats receiving all treatments but limited to a few animals per treatment group can be used for pharmacokinetic/toxicokinetic measurements, or a satellite group containing all treatment groups but only receiving a single dose can be used to examine acute effects in a subchronic repeat dose study.

UF Uncertainty Factors. Typically UFs are intended to account for uncertainty in extrapolating animal data to humans (inter-species variability), the variation in sensitivity among humans (inter-individual variability), quality of data, severity of response, or other concerns, where available sources of variability can be replaced with chemical specific information to refine the UF, such as toxicokinetics, toxicodynamics, QSAR, MOA, and information on closely related compounds.

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5. *Annex 1 - Procedure for the Derivation of an Appropriate ARfD*